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From the
INTERNATIONAL SEARCHING AUTHORITYDocket No: PR 60711 WO
Attorney: JPSY
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WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43bis.1)Date of mailing 07/07/2005
(day/month/year) see form PCT/ISA/210 (second sheet)Applicant's or agent's file reference
see form PCT/ISA/220FOR FURTHER ACTION
See paragraph 2 belowInternational application No.
PCT/US2005/005467International filing date (day/month/year)
22.02.2005Priority date (day/month/year)
25.02.2004International Patent Classification (IPC) or both national classification and IPC
C07D215/36, C07D215/22, A61K31/4709, A61P35/00Applicant
SMITHKLINE BEECHAM CORPORATION

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**International application No.
PCT/US2005/005467**Box No. I Basis of the opinion**

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ in written format
 - ☐ in computer readable form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**International application No.
PCT/US2005/005467**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
☒ claims Nos. 1-27

because:

- ☒ the said international application, or the said claims Nos. 24-27 (with respect to industrial application) relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

- ☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 1-27 (in part) are so unclear that no meaningful opinion could be formed (*specify*):

see separate sheet

- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
☐ no international search report has been established for the whole application or for said claims Nos.
☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form ☐ has not been furnished

☐ does not comply with the standard

the computer readable form ☐ has not been furnished

☐ does not comply with the standard

- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.

- ☐ See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**International application No.
PCT/US2005/005467

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

| | | |
|-------------------------------|-------------|------|
| Novelty (N) | Yes: Claims | 1-27 |
| | No: Claims | |
| Inventive step (IS) | Yes: Claims | 1-27 |
| | No: Claims | |
| Industrial applicability (IA) | Yes: Claims | 1-23 |
| | No: Claims | |

2. Citations and explanations**see separate sheet**

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/US2005/005467

Re Item III.

The application does not meet the requirements of Article 6 PCT, because claims 1-27 are not clear.

The term "pharmaceutically acceptable derivative" in claim 1 of the present application is not a well defined technical feature and renders the scope of the said claim unclear. The dependent claims are also unclear because of this term.

Claims 24-27 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V.

- 1 Reference is made to the following document:
D1 : WO 02/094788 A (ELI LILLY AND COMPANY; WALLACE, OWEN,
BRENDAN) 28 November 2002 (2002-11-28)

2. Document D1, which is considered to represent the most relevant state of the art, discloses 2-substituted 1,2,3,4-tetrahydroquinolines for use as estrogen receptor modulator.

From this, the subject-matter of independent claim 1 differs in that:

- a) a tetrahydroquinoline is used
- b) the substituted X-phenyl group is connected to the nitrogen of the quinoline whereas in the present application this group is connected on the 4-position of the quinoline ring.
- c) the substituted phenyl group is conned on the 2-position of the tetrahydroquinoline ring whereas in the present application this group is found in position 3.

2.1 The subject-matter of claim 1 is therefore novel (Article 33(2) PCT)
The problem to be solved by the present invention may be regarded as:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/US2005/005467

The provision of alternative compounds for the modulation of estrogen receptors.

2.2 The solution to this problem proposed in claim 1 of the present application is considered as involving an inventive step (Article 33(3) PCT) for the following reasons: A skilled person would not, starting from D1, change 3 different features in the molecules. It is therefore considered that the subject-matter of claim 1 of the present application is inventive over the prior art.

2.3 Claims 2-15 and 18-20 are dependent on claim 1 and as such also meet the requirements of the PCT with respect to novelty and inventive step.

3 Claims 16 and 17 are about pharmaceutical compositions of inventive compounds of formula (I) of the present application. These claims are also considered inventive.

4 Claims 21-27 are about the use of inventive compounds of formula (I) for the preparation of medicaments against diseases related to estrogen receptors. The use is also considered inventive over the prior art.